ELSEVIER

Smoking Cessation and Renal Cell Carcinoma

ALEXANDER S. PARKER, PHD, JAMES R. CERHAN, MD, PHD, CAROL A. JANNEY, MS, CHARLES F. LYNCH, MD, PHD, AND KENNETH P. CANTOR, PHD

PURPOSE: The magnitude and timing of the reported decrease in risk of renal cell carcinoma (RCC) attributed to smoking cessation is not well characterized. Furthermore, conclusions from previous investigations have been hampered by unstable risk estimates, broad exposure categories and/or insufficient adjustment for the inverse correlation of cessation years with lifetime smoking exposure.
METHODS: To address these issues, we report data from a population-based case-control study conducted in Iowa from 1986 to 1989. RCC cases (n = 387) were identified through the Iowa Cancer Registry, while controls (n = 2,333) were randomly selected from the general population, frequency-matched on age and sex. Subjects provided detailed information on a mailed questionnaire regarding their smoking history as well as other anthropometric, lifestyle, dietary and medical history risk factors.
RESULTS: Smoothing spline regression analysis provided evidence of a consistent inverse linear trend between years of cessation and risk of RCC. In categorical analysis, compared with current smokers, those quitting ⩾30 years ago experienced a 50% reduction in risk of RCC (OR = 0.5; 95% CI 0.3 to 0.8) after adjustment for age, sex, BMI, hypertension and pack-years of smoking. Risk among long-term quitters was similar to risk among never smokers (OR = 0.6; 95% CI 0.4 to 0.8). In contrast, cessation of <10 years, 10 to 19 years and 20 to 29 years all resulted in a less pronounced reduction in RCC risk (∼20% to 30%).
CONCLUSIONS: Our findings suggest that while cessation of smoking is indeed associated with a linear decrease in RCC risk even after adjustment for potential confounders, this benefit may not be sizeable until more than 20 years following cessation.
Ann Epidemiol 2003;13:245–251.

KEY WORDS: Smoking Cessation, Case-Control, Renal Cell Carcinoma, Smoothing Spline Regression, Generalized Additive Models, GAM.

INTRODUCTION

Guidelines from both the American Cancer Society and the National Cancer Institute advise that smoking cessation lowers the risk of renal cell carcinoma (RCC) (1, 2). However, evidence from the literature supporting this claim is not consistent (3–7). Complicating matters further, results from the small number of available investigations are often difficult to interpret due to specific limitations. These limitations include imprecise risk estimates (especially in extreme categories) as well as failure to adjust adequately for lifetime smoking exposure. In addition, previous studies have been limited by the exclusive use of categorical analysis to evaluate this association. We are unaware of any attempt to supplement categorical analysis with more sophisticated regression methods (i.e. generalized additive models) that analyze years of smoking cessation as a continuous variable and thus avoid the potential loss of information and power associated with categorical analysis (8, 9). Finally, to our knowledge there has been no effort to determine whether other known risk factors for RCC modify the effect of smoking cessation on RCC risk.

The primary objective of this investigation was to characterize the association of smoking cessation and RCC development in a Midwestern US population after adjustment for accepted RCC risk factors, including lifetime pack-years of smoking. In secondary analysis, we assessed whether the association of smoking cessation and RCC risk is uniform across levels of other known risk factors for RCC (i.e. gender, body mass index and hypertension). To do this, we used data from a population-based case-control investigation conducted in Iowa from 1986 to 1989.

MATERIALS AND METHODS

Study Population

Full details of this study are reported elsewhere (10). Briefly, we conducted a population-based case-control in-

From the Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN (A.S.P., J.R.C., C.A.J.); Department of Epidemiology, School of Public Health, University of Iowa, Iowa City, IA (C.F.L.); and Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard EPS-8106, Bethesda, MD 20892 (K.P.C.).

Address correspondences to: Alexander S. Parker, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel.: (507) 266-2928; Fax: (507) 266-2478. E-mail: parker.alexander@mayo.edu

Received November 6, 2001; revised April 4, 2002; accepted April 4, 2002.

1047-2797/03/$–see front matter
PII S1047-2797(02)00271-5

AEP Vol. 13, No. 4
April 2003: 245–251

Selected Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
GAM = generalized linear model
ICR = Iowa Cancer Registry
OR = odds ratio
RCC = renal cell carcinoma

vestigation of cancer occurrence at six anatomic sites (pancreas, bladder, kidney, brain, colon, and rectum). Cases of RCC (ICD-O code 189.0) were identified from 1985 to 1987 by the Iowa Cancer Registry (ICR), a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (11). This program was supplemented by a rapid reporting system in 1987. Eligible cases were residents of the state of Iowa, age 40 to 85, and newly diagnosed with histologically confirmed RCC. No independent pathology review was performed. Those with a previous diagnosis of a malignant neoplasm, except basal and squamous cell carcinomas of the skin, were excluded. Of the 463 incident RCCs identified for the study, 406 (88 percent) responded, with 93 (22 percent) requiring proxy respondents to provide information.

Control subjects under the age of 65 were randomly selected from computerized state driver's license records while controls ages 65 and older were selected randomly from listings provided by the US Health Care Financing Administration (HCFA). Both of these selection rosters provide excellent coverage of the state population (12, 13). As with the cases, controls with a history of cancer, except non-melanoma skin cancer, were excluded. Controls were frequency matched to cases by gender and 5-year age group. Of the 999 control subjects under the age of 65 identified, 817 (82 percent) participated while 1617 of 2036 (79 percent) of identified controls 65 years and over participated. Only two control subjects required proxy respondents.

Data Collection

Data were collected using a mailed questionnaire, which included inquiries regarding risk factors for RCC such as demographics, anthropometric measures at various times in life, smoking history and status (including age at cessation, if applicable), medical history, reproductive factors, occupational history, usual physical activity (non-occupational) and family history of cancer (14). Also included in the questionnaire was a 55-item food frequency section. Subjects who were reluctant to complete the detailed questionnaire were offered a 15-minute abbreviated telephone interview that excluded the detailed occupational history and food frequency sections.

Information on smoking cessation was ascertained from responses to the section of the questionnaire regarding the use of tobacco products. Individuals who responded that they had never used any tobacco product for six months or longer were classified as never smokers. Current smokers were defined as anyone who reported smoking cigarettes for a continuous period of six months or longer and additionally that they were smoking within the two years preceding cancer diagnosis (cases) or return of the questionnaire (controls). Any individuals reporting that they had quit smoking two or more years prior to cancer diagnosis (cases) or return of the questionnaire (controls) were classified as former smokers. Among these former smokers, the number of years since the termination of smoking was determined by subtracting the reported age at which they had stopped smoking from their age at the time they entered the study.

Statistical Analysis

After excluding subjects who lacked information on smoking history (19 cases, 101 controls), there were 387 cases of RCC and 2333 controls available for this analysis. Smoking cessation was analyzed as both a continuous and a categorical variable. For any analysis utilizing the continuous form of smoking cessation years, current smokers were given a value of zero and never smokers were specified as missing and therefore removed from analysis. After reviewing information from previous studies and the distribution among our control subjects, the following ordinal variable for smoking cessation was created: 0 = current smoker, 1 = former smoker who quit <10 years ago, 2 = former smoker who quit 10 to 19 years ago, 3 = former smoker who quit 20 to 29 years ago, 4 = former smoker who quit 30 or more years ago and 5 = never smoker. This categorization allowed for risk estimates to be calculated in reference to current smoking and additionally permitted indirect comparisons with never smokers as well. Since similar findings were noted in the analysis of cessation years as either a continuous or categorical variable, we report the results for cessation years as a categorical variable for ease of interpretation.

Odds ratios (OR) and 95 percent confidence intervals (CI) were used to estimate the association of smoking cessation and RCC. We employed unconditional logistic regression to estimate both age-adjusted as well as multivariate-adjusted ORs. The following covariates were included in multivariate analysis: sex, body mass index (kg/m^2), hypertension (self-report of physician diagnosis, yes/no), pack-years of smoking (continuous), family history of kidney cancer (1st degree relative), non-occupational physical activity, history of bladder infection and dietary intake of red meat, fruit and vegetables. The choice of variables for the final multivariate model was based on whether or not inclusion of the covariate resulted in at least a 10% change in the estimated ORs. The final multivariate model included age, sex, body mass index, history of hypertension

and pack-years of smoking. Formal tests of trend were performed using both the continuous form of the smoking cessation variable as well as the ordinal score variable with the referent category removed. No differences were noted between the two methods, therefore we report results based on the tests involving the ordinal score variable. Effect modification by each of the covariates considered in the final multivariate analysis was evaluated by stratifying on the variable of interest and comparing the ORs within each stratum. Formal tests for effect modification were performed by including an interaction term, along with the main effects, in the regression model. To assess the potential for bias due to next-of-kin respondents, we repeated our analysis excluding the 93 cases and 2 controls with proxy data. No differences were noted in the risk estimates, so we report the data using the entire study group.

An underlying assumption of logistic regression is that the logit of RCC risk on cessation years is linear. To test this linearity assumption and to assess the appropriate functional form for cessation years, we fit generalized additive models (GAMs) for RCC with cessation years modeled as a smoothing spline with 4 degrees of freedom. Statistical analyses were performed using the PROC LOGISTIC procedure in SAS version 8.2 (SAS Institute; Cary, NC) and Splus for GAM models (Mathsoft, Inc., Seattle, WA).

RESULTS

Table 1 presents the distribution of potential confounding factors across categories of smoking cessation among the control group. Differences in both age and gender were noted across levels of smoking cessation, with long term quitters (20 to 29 years and 30+ years) being slightly older and more likely to be male than both current smokers and those that had quit smoking within 10 years of baseline. As expected, individuals who reported having quit smoking for 20 to 29 years or more than 30 years had substantially fewer overall pack-years of smoking than current smokers or shorter term quitters (quit within 10 years of baseline). Further, calculation of a Pearson correlation coefficient between years of smoking cessation and total pack-years of smoking among former smokers revealed an inverse relationship between the two variables ($r = -0.55$; $p < 0.0001$). Current smokers were in general leaner than those who had stopped smoking. Nevertheless, among those who had quit smoking, there was very little difference in reported BMI across the cessation categories (i.e <10 years, 10 to 19 years, 20 to 29 years and 30+ years). Finally, compared with current smokers, a reported history of hypertension was more common among those who had quit smoking. However, as was the case with BMI, there was little difference in reported history of hypertension when comparisons were made between the different cessation categories.

As displayed in Figure 1, the linearity assumption for the logistic regression model was tenable for cessation years and RCC (a straight line easily fits within the confidence intervals; formal test for departure from linearity was non-significant, $p = 0.3$). Specifically, a decreasing linear association was observed between RCC risk and cessation years as a continuous variable. Due to a small number of people who

TABLE 1. Distribution of selected risk factors among controls by years of smoking cessation, Iowa, 1986 to 1989

	Smoking Status						
Risk Factors	Current smoker (n = 465)	Quit < 10 years ago (n = 184)	Quit 10–19 years ago (n = 243)	Quit 20–29 years ago (n = 241)	Quit ⩾ 30 years ago (n = 191)	Never smoked (n = 1,009)	p-value[a]
Age (mean, in years)	64.0	67.8	68.1	69.3	72.5	69.1	0.0001
Gender							
Male	70.0%	76.7%	86.4%	90.1%	90.0%	43.1%	
Female	30.0%	23.3%	13.6%	9.9%	10.0%	56.9%	0.0001
Pack-years of smoking							
None	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	
1–20	11.2%	8.8%	22.6%	37.9%	73.3%	0.0%	
21–39	23.5%	20.7%	30.2%	39.0%	20.4%	0.0%	
40+	65.4%	70.5%	47.2%	23.1%	6.3%	0.0%	0.0001
BMI (kg/m^2)							
<24	49.4%	35.6%	32.7%	35.6%	28.4%	36.4%	
24–29	25.3%	29.3%	29.7%	30.0%	41.1%	30.6%	
>29	25.3%	35.1%	37.6%	33.4%	30.5%	33.0%	0.0001
History of hypertension							
No	71.4%	63.9%	62.0%	61.4%	62.6%	60.6%	
Yes	28.6%	37.1%	38.0%	39.6%	37.4%	39.4%	0.0001

[a]p-value is either for global test for differences among means or chi-square test for differences in proportions, as appropriate.

AEP Vol. 13, No. 4
April 2003: 245–251

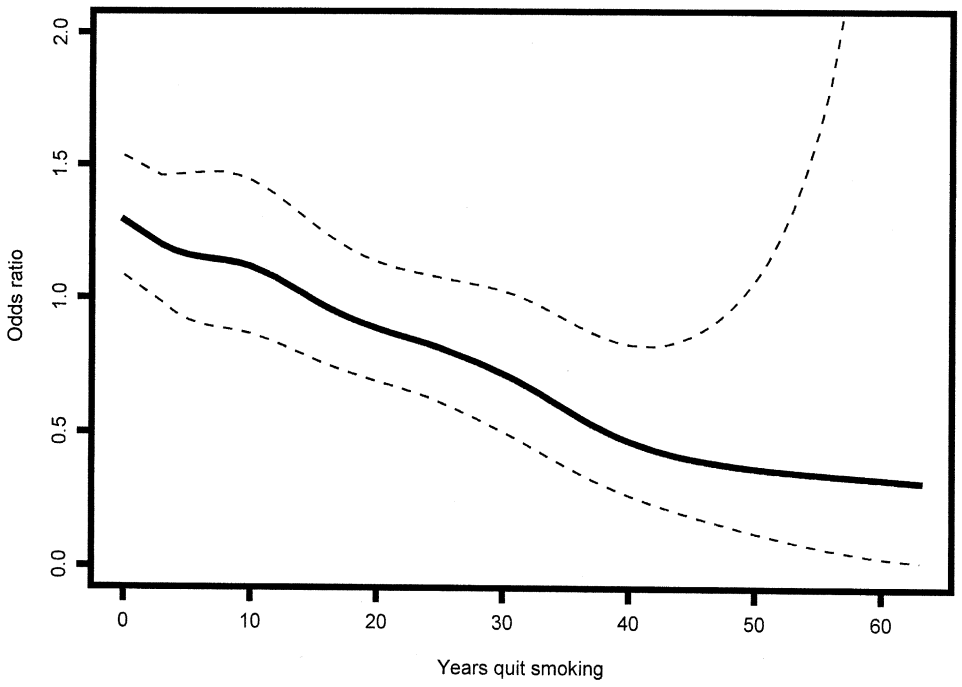

FIGURE 1. Association [odds ratio (solid line) and 95% CI (dotted lines)] of cessation years with risk of renal cell cancer in a univariate GAM model controlling for age, BMI, hypertension and pack years of smoking. Current smokers have a value of zero for cessation years and never smokers are excluded from the analyses.

stopped smoking for more than 40 years, wide confidence intervals were observed for cessation years greater than 40. Conversely on the left-hand side of the curve, there is a slight narrowing of the confidence intervals due to the relatively large number of current smokers that were coded as having zero years of smoking cessation.

Age and multivariate-adjusted estimates of the risk associated with the different categories of smoking cessation are provided in Table 2. After adjustment for age, there was evidence of a slight decrease in RCC risk for those who reported <10 years and 10 to 19 years since smoking cessation (~20% for each). In contrast, cessation of 20 to 29 years (OR = 0.6; 95% CI 0.4 to 1.0) and 30 or more years (OR = 0.5; 95% CI 0.3 to 0.8) both resulted in reductions in age-adjusted RCC risk to a level that was comparable to that of never smokers (OR = 0.6; 95% CI 0.4 to 0.8). Multivariate adjustment for age, sex, BMI, hypertension and pack-years of smoking resulted in the same 50% reduction for long-term quitters (30 or more years) but slightly attenuated the risk reduction for those reporting 20 to 29 years since cessation (OR = 0.7; 95% CI 0.4 to 1.1). The RCC risk estimate for those reporting 10 to 19 years since cessation was unaffected by multivariate adjustment, however the magnitude of the association with short-term quitters (<10 years) strengthened slightly (OR = 0.7; 95% CI 0.4 to 1.1). In both age-adjusted and multivariate analyses, formal tests for trend using the ordinal score variable or the continuous form of cessation years confirmed the decreasing risk with increasing years of cessation ($p < 0.0001$) that was identified using spline regression.

While there was no evidence that gender, BMI or total pack-years modified the effect associated with smoking cessation, we did note that the relationship between years of smoking cessation and RCC risk may not be uniform across categories of history of hypertension (p for interaction = 0.03). Table 3 contains stratum-specific estimates of RCC-risk associated with smoking cessation for normotensives and hypertensive individuals. Among normotensive individuals, we found a pattern of risk estimates very similar to that reported for the overall analysis. In fact, the magnitude of the risk reduction associated with years of smoking cessation, especially among the long-term smokers, was slightly stronger in this subgroup ($OR_{30+\ years} = 0.2$; 95% CI 0.1 to 0.5). Conversely, among those who reported a history of hypertension, the association was attenuated ($OR_{30+\ years} = 0.9$; 95% CI 0.4 to 1.8) and there was little evidence of a trend with increasing cessation years ($p = 0.5$). Multivariate adjustment did not alter the results of this stratified analysis.

DISCUSSION

Evidence from this population-based case-control investigation suggests that long-term smoking cessation (20 or more years) reduces the risk of RCC to a level that is equal to that of never-smokers, even after adjustment for lifetime smoking intensity and duration. Shorter cessation periods (<10 years, 10 to 19 years) were associated with only moderate reductions in RCC risk. Smoothing spline modeling

TABLE 2. Age adjusted and multivariate risks of RCC according to years of smoking cessation, Iowa, 1986 to 1989

	Overall					
	Cases	Controls	OR[a]	95% CI	OR[b]	95% CI
Years of cessation						
Current smoker	123	465	1.0	—	1.0	—
<10 years	36	184	0.8	0.5–1.3	0.7	0.4–1.1
10–19 years	47	243	0.8	0.5–1.1	0.8	0.5–1.2
20–29 years	31	241	0.6	0.4–1.0	0.7	0.4–1.1
⩾30 years	18	191	0.5	0.3–0.8	0.5	0.3–1.0
Never smokers	132	1,009	0.6	0.4–0.8	0.6	0.4–0.9
p trend[c]				0.0001		0.005

[a]Adjusted for Age.
[b]Adjusted for Age, Sex, Body Mass Index (kg/m ^{2}), Hypertension and Pack-years of Smoking.
[c]Test performed with reference category removed from ordinal score variable. Tests using continuous form of years of cessation produced similar trend test results.

TABLE 3. Age-adjusted and multivariate risks of RCC according to years of smoking cessation, stratified by self-report of Physician-diagnosed hypertension, Iowa, 1986 to 1989

	Normotensives only					
	Cases	Controls	OR [a]	95% CI	OR [b]	95% CI
Years of cessation						
Current smoker	75	313	1.0	—	1.0	—
<10 years	17	113	0.7	0.4–1.2	0.7	0.4–1.1
10–19 years	30	144	0.9	0.6–1.5	1.0	0.6–1.8
20–29 years	5	137	0.2	0.1–0.5	0.2	0.1–0.6
⩾30 years	4	114	0.2	0.1–0.5	0.3	0.1–0.8
Never smokers	54	553	0.4	0.3–0.6	0.6	0.4–1.0
p trend[c]				0.0001		0.02
	Hypertensives only					
	Cases	Controls	OR [a]	95% CI	OR [b]	95% CI
Years of cessation						
Current smoker	37	118	1.0	–	1.0	–
<10 years	14	66	0.8	0.4–1.6	0.8	0.4–1.7
10–19 years	15	87	0.7	0.4–1.4	0.7	0.4–1.4
20–29 years	25	86	1.2	0.7–2.2	1.2	0.6–2.2
⩾30 years	13	68	0.9	0.4–1.8	0.9	0.4–2.0
Never smokers	68	360	0.8	0.5–1.3	0.6	0.3–1.1
p trend[c]				0.5		0.2

[a]Adjusted for Age.
[b]Adjusted for Age, Sex, Body Mass Index (kg/m^2), and Pack-years of Smoking.
[c]Test performed with reference category removed from ordinal score variable. Tests using continuous form of years of cessation produced similar trend test results.

suggested the existence of a linear trend of decreasing risk with increasing years of smoking cessation. Multivariate adjustment for other risk factors for RCC development did not alter our results. We found no evidence that the reduction in risk associated with smoking cessation differed according to gender, BMI or pack-years of smoking. We also report preliminary data suggesting that the reduction in RCC risk may be apparent only among those individuals with no history of hypertension.

Two previous studies have assessed the association of smoking cessation and RCC risk after adjustment for pack-years of smoking, however data from each is somewhat limited (3, 5). In a Danish study involving 178 cases and 181 controls, Mellemgaard et al (3), reported no evidence of a decrease in RCC risk with increasing duration of smoking cessation after adjustment for age, socioeconomic status, BMI and cigarette pack-years. In fact, the authors reported an unexpected increase in risk for only those individuals with 10 to 14 years of cessation (OR = 3.3; 95% CI 1.3 to 7.9). Conclusions from this investigation however, were limited due to small numbers of cases in most categories. In addition, the authors chose a broad upper category of cessation years (15+ years) that may have masked a true effect at higher levels. In a population-based case-control study conducted in New South Wales, McCredie and Stewart (5) reported that while there was a dose-response association between pack-years of smoking and RCC risk among those who had quit for 25 years or less, there was no such evidence among those who quit for more than 25 years. However, estimates among the long-term quitters (25+ years) were imprecise due to the small numbers of individuals with high levels of smoking pack-years. Of interest, the largest case-control study to date on smoking and RCC (1,732 cases, 2,309 controls) provided evidence of only a slight decrease in RCC risk associated with smoking cessation (6). Those individuals who reported more than 25 years of smoking cessation were at slightly lower RCC risk compared with current smokers (OR = 0.85; 95% CI 0.6 to 1.1), after adjustment for age, sex, BMI and number of cigarettes per day. Two other case-control investigations in Canada (4) and California (7), provided evidence of a small decrease in risk for the highest category of smoking cessation (20+ years). In both studies, however, no adjustment was made for pack-years of smoking and the risk estimates lacked precision.

Categorization of continuous exposure data has the advantage of simplifying the interpretation of epidemiologic results. However, drawbacks of this method include possible bias due to the choice of cutpoints as well as the potential for loss of information due to the averaging of risks across broad categories that may be biologically irrelevant (8, 9). Linear models that utilize continuous forms of data avoid the disadvantages associated with categorization mentioned above. However, such models assume a linear parametric response that may not be appropriate (15). In contrast to parametric models, generalized additive models (GAMs) do not assume linearity between the risk factor and the outcome, thus permitting the flexible modeling of the risk factor as a continuous smooth function (16–19). In

this study, we utilized GAMs to check the linearity assumption between cessation years and RCC risk, and to determine the appropriate functional form of the exposure/outcome relationship. As displayed in Figure 1, there was no evidence of a non-linear association between cessation years and RCC risk. Further, because there was evidence of a consistent, monotonic decrease in risk with duration of cessation, it is very unlikely that our choice of categorization cutpoints masked the true effect.

Our analysis suggests that the reduction in RCC risk associated with smoking cessation is apparent among normotensive individuals only. Extreme caution however should be used when interpreting this particular result, as we cannot completely rule out the role of chance. Hypertension among participants was based on self-report of a medical diagnosis and did not include information on timing and/or severity of the condition. Of interest, there is data from this same case-control investigation that suggests smoking is a risk factor among normotensive but not hypertensive individuals (20). However, barriers to the interpretation of this finding include the validity of self-reported hypertension data, confounding by hypertensive medication use and the lack of a plausible biologic mechanism. Confirmation in future investigations is needed.

Strengths of this study include the use of population-based cases and controls, high participation rates for both groups, detailed individual data on potential confounders and the use of advanced modeling techniques (smoothing spline regression) to support the assumption of linearity in the logit. However, there are also limitations to these data. The minimum value for smoking cessation years among former smokers in this population was 3 years, thus we are unable to extrapolate risk estimates from our <10 years category to individuals who have only recently stopped smoking. However, an argument can be made that these individuals (recent quitters) should be removed from analysis anyway due to the potential for subclinical disease to alter lifestyle habits. Of more concern is the correlation between pack-years and smoking cessation years. Although we have adjusted for pack-years in our analysis, some residual confounding may still exist given the correlation between these two variables. We found no evidence of an interaction between pack-years and smoking cessation, suggesting that the effect was similar for light and heavy lifetime smokers. However, failure to detect this interaction statistically could have been due to limited study power. Other limitations include low generalizability, self-reported BMI and history of hypertension as well as small case numbers in some hypertension strata.

Data from this population-based case-control investigation support the recommendation that smoking cessation lowers the risk of RCC, even after controlling for lifetime smoking exposure. Further, we suggest that the risk of RCC among former smokers can eventually be lowered to a level similar to never smokers but only after long term cessation (more than 20 years). Our modeling of the risk curve using smoothing spline regression is novel and further strengthens the evidence of a true inverse linear association between smoking cessation and RCC risk.

This work was supported by National Cancer Institute contracts NCI-NO1-CP-5106 and NCI-NO1-CP-85614. Dr. Parker was supported in part by the Cancer Research Foundation of America's Cancer Prevention Research Fellowship. Dr. Cerhan was supported in part by a National Cancer Institute Preventive Oncology Academic Award. We thank Doretta Johnson and Nyla Logsden–Sackett for coordination of data collection activities and Dan Olson for preparation and editing of digitized subject data at the University of Iowa.

REFERENCES

1. American Cancer Society. What causes kidney cancer? Can it be prevented? Available from: www.cancer.org. Accessed June 24, 2002.
2. National Cancer Institute. What you need to know about kidney cancer. Information about detection, symptoms, diagnosis, and treatment of kidney caner. NIH Publication No. 96–1569. Available from: www.nci.nih.gov. Accessed June 24, 2002.
3. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. Cancer Causes Control. 1994;5:105–113.
4. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. Cancer Causes Control. 1993;4:101–110.
5. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales–I. Cigarette smoking. Eur J Cancer. 1992;28A:2050–2054.
6. McLaughlin JK, Lindblad P, Mellemgaard A. McCredie M, Mandel JS, Schlehofer B, et al. International renal-cell cancer study. I. Tobacco use. Int J Cancer. 1995;60:194–198.
7. Yuan JM, Castelao JE, Gago–Dominguez M, Yu MC, Ross RK. Tobacco use in relation to renal cell carcinoma. Cancer Epidemiol. Biomarkers & Prev. 1998;7:429–433.
8. Greenland S. Avoiding power loss associated with categorization and ordinal scores in dose–response and trend analysis. Epidemiology. 1995;6:450–454.
9. Weinberg CR. How bad is categorization? Epidemiology. 1995;6:345–347.
10. Chiu BC-H, Lynch CF, Cerhan JR, Cantor KP. Cigarette smoking and risk of bladder, pancreas, kidney and colorectal cancers in Iowa. Ann Epidemiol. 2001;11:28–37.
11. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973 to 1997, with a special section on colorectal cancer. Cancer. 2000; 88:2398–2424.
12. Hartge P, Cahill JI, West D, Hauck M, Austin D, Silverman D. et al. Design and methods in a multi-center case-control interview study. Am J Public Health. 1984;74:52–56.
13. Lynch CF, Logsden-Sackett N, Edwards SL, Cantor KP. The driver's license list as a population-based sampling frame in Iowa. Am J Public Health. 1994;84:469–472.
14. McLaughlin JK, Lipworth L. Epidemiologic aspects of Renal Cell Cancer. Semin Oncol. 2000;27:115–123.
15. Rothman KJ, Greenland S, eds. Modern Epidemiology. 2nd edition. Philadelphia, PA: Lippincott-Raven, 1998.
16. Abrahamowicz M, du Berger R, Grover SA. Flexible modeling of the effects of serum cholesterol on coronary heart disease mortality. Am J Epidemiol. 1997;145:714–729.

17. Zhao LP, Kristal AR, White E. Estimating relative risk functions in case-control studies using a nonparametric logistic regression. Am J Epidemiol. 1996;144:598–609.
18. Figueiras A, Cadarso-Suarez C. Application of nonparametric models for calculating odds ratios and their confidence intervals for continuous exposures. Am J Epidemiol. 2001;154:264–275.
19. Hastie TJ, Tibshirani RJ. Generalized Additive Models. New York: Chapman and Hall, 1990.
20. Beane Freeman LE, Parker AS, Lynch CF, Cantor KP. Smoking, Renal Cell Carcinoma and Effect Modification by History of Hypertension. Abstract for Society of Epidemiologic Research. Seattle, Washington. June, 2000.